Indiana Veteran Recovery Study

...a Multicenter Study of Hyperbaric Oxygen Therapy (HBOT) at Low Pressure in Chronic Traumatic Brain Injury (TBI)/Post-Concussion Syndrome (PCS) and TBI/Post-Traumatic Stress Disorder (PTSD)

Principle Investigator /program director:

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Where work will be performed:

All work will be conducted at Riverview Hospital in Noblesville, Indiana and up to three (3) other Indiana Hospitals to be determined. All hospitals in the study currently operate hyperbaric chambers meeting all state and federal regulations. Determination will be made after negotiation and acceptance of the conditions and specifications identified in this study by the additional hospitals. Total individuals to be evaluated during this study is 150.

Total Budget: $1,003,650.00

Cost Estimate for 150 Patient Study Population for 2 years

Latest Update: August 2016

		Riverview		Site 2		Site 3		Site 4		
		YEAR 1	YEAR 2	YEAR 1	YEAR 2	YEAR 1	YEAR 2	YEAR 1	YEAR 2	
PATIENTS TO BE TREATED	Rate	20	30	15	20	15	20	15	15	150
HBOT Treatments										
40 dives	5600	112,000	168,000	84,000	112,000	84,000	112,000	84,000	84,000	
Inclusion/Exclusion Criteria/Informed Consent	60	1,200	1,800	900	1,200	900	1,200	900	900	
Medical History and Demography	160	3,600	4,800	2,400	3,200	2,400	3,200	2,400	2,400	
Tests and documents prior to first treatment	180	3,600	5,400	2,700	3,600	2,700	3,600	2,700	2,700	
Tests and documents at treatment 20	60	1,200	1,800	900	1,200	900	1,200	900	900	
Tests and documents at treatment 40	60	1,200	1,800	900	1,200	900	1,200	900	900	
6 month follow-up	60	1,200	1,800	900	1,200	900	1,200	900	900	
12 month follow-up	60	1,200	1,800	900	1,200	900	1,200	900	900	
24 month follow-up	60	1,200	1,800	900	1,200	900	1,200	900	900	
Adverse Events 0.01 PERSON	1	20	30	15	20	15	20	15	15	
CRF Completion (Case Report Form)	30	600	900	450	600	450	600	450	450	
Diagnostics										
ANAM License and Fees ($20 per use) X total 3 uses	60	1,200	1,800	900	1,200	900	1,200	900	900	0-20-40 DIVES
CNS-VS License & Fees ($20 per use) X total 3 uses	60	1,200	1,800	900	1,200	900	80	900	900	0-20-40 DIVES
Blood work (2 draws X $75/draw)	150	3,000	4,500	2,250	3,000	2,250	3,000	2,250	2,250	2 DRAWS (BEFORE & AFTER)
Imaging @ $2,000/image X total 3	0									NOT MANDITORY SPECT OR CERESCAN
Trans-cranial doppler test @ $200 X total 3	0									Additional Data points
		127,020	**189,930**	**94,965**	**126,620**	**94,965**	**126,620**	**94,965**	**94,965**	**$ 950,050.00**

FIXED COSTS				
Facility				
Office Space		0.00	0.00	Existing hospital facilities will be used at no additional expense to project.
Office Furniture & Equipment		0.00	0.00	Existing hospital facilities will be used at no additional expense to project.
Office Supply		0.00	0.00	Existing hospital facilities will be used at no additional expense to project.
Storage		0.00	0.00	Existing hospital facilities will be used at no additional expense to project.
Cable and Internet		0.00	0.00	Existing hospital facilities will be used at no additional expense to project.
Office Phone and Fax		0.00	0.00	Existing hospital facilities will be used at no additional expense to project.
Professional Fees				
Bookkeeping		3000.00	3000.00	Person to track funds used against funds on hand.
Statistical and Analytical Support		12000.00	12000.00	Don Berry -- IHBF consultant
Staff				
Executive Director		0.00	0.00	Covered by Riverview Hospital & other hospitals
Exec Asst / Secretary		0.00	0.00	Covered by Riverview Hospital & other hospitals
I.T. System Admin/Help Desk		0.00	0.00	Covered by Riverview Hospital & other hospitals
Assistant Director / Operations Officer		0.00	0.00	Covered by Riverview Hospital & other hospitals
Public Relations and Marketing		0.00	0.00	TMVCI volunteers and PI will provide free
Staff Psychologist/Social Worker/Case Officer		0.00	0.00	Covered by Riverview Hospital & other hospitals
Travel		2000.00	0.00	Rob Beckman to come and train on software.
Investigators				
Administrative Primary Investigator:		0.00	0.00	Covered by Riverview Hospital & other hospitals
Scientific Primary Investigator:		0.00	0.00	Covered by Riverview Hospital & other hospitals
Medical Monitor / HRP Associates		0.00	0.00	Covered by Riverview Hospital & other hospitals
Administration & On-Going Support				
Data Safety Monitoring Board		0.00	0.00	INSTUTUTIONAL REVIEW BOARD of Riverview & other hospitals
Initial Site Start-ups & Visits		0.00	0.00	Jim BAUERLE & ROB BECKMAN
Site Medical Monitor		0.00	0.00	PI to perform these duties
Call Center for Tier 1 Support and Help Desk		0.00	0.00	JIM BAUERLE PHONE NUMBER
Periodic Support and Miscellaneous				
Human Research Protection Consulting Fees		0.00	0.00	RIVERVIEW HAS --HIPA REGS FOLLOWED
CITI License		0.00		MUST BE CT QUALIFIED -- PEOPLE COLLECTING DATA Hospital already have
Care Vector (Master Data Base)				
Infrastructure and Hosting		10800.00	10800.00	MONTHLY RENTAL OF $900
Living and Travel Arrangements				staff performing research will not need to travel
TOTAL		**27,800**	**25,800**	**GRAND TOTAL $1,003,650.00**

Program Description:

1. The health care clinic to be used is Riverview Hospital:
    a. Which meets the Section 501 IRS code.
    b. Employs doctors and physical therapists licensed in Indiana under IC 25-27.
    c. Treats patients with long term, chronically ill, and short term care needs.
2. This clinical trial has proven significant and sustained improvement to individuals with brain injuries in Israel, and as used in application and trials in the United States. This study intends to address the use of hyperbaric oxygen therapy at 1.5 atmospheric pressure to significantly improve patients suffering the debilitating effects of traumatic brain injury, post traumatic stress "disorder", and other post concussive brain insults.
    a. Staffing:
        i. Staffing for this clinical trial will include doctors and registered nurses trained in the application of hyperbaric oxygen therapy; hyperbaric chamber technicians trained and certified in accordance with federal and state regulations, medical clinicians certified and licensed to administer drugs as needed.
        ii. Ratio of staff to projected number of persons served may vary but usually will be an office worker, technician, doctor, and nurse treating up to two patients per site at a time.
    b. Patient selection process:

Subjects will be 18-65 years old and have been diagnosed with mild or moderate (but not severe) TBI or TBI/PTSD or PTSD by either the military (any etiology) or civilian neurologists or neuropsychologists. This diagnosis will especially include war veterans who have received the ANAM test pre- and post-deployment and had a significant decrease in their neuropsychological test scores.

Gender Restrictions

There will be no gender restrictions. However, it is anticipated that the cohort will consist mostly of males, due to the nature of the injury and the preponderance of men in the military serving in combat arms units.

Racial & Ethnic Origin

The demographics of the study subjects will likely mirror the demographics of the military since the study will likely have a high proportion of military TBI subjects. The military has a high minority representation. No attempt will be made to limit minority involvement in the study nor will attempt to target particular minorities for enrollment.

Subjects will be enrolled who meet study criteria regardless of etiology of injury, race, or other discriminatory factors, including gender. Though there has been a preponderance of injury in the combat arms units, where nearly 100% of veterans report at least one concussive injury, about 50% of the Combat Support and Combat Service Support (like transportation and water purification and military police) report having had at least one concussive blast. This is expected to create a large cohort of female patients in the larger study, especially including the National Guard, because of the makeup of those units. We expect the study to include more men than women, but there should be a sufficient number of women to gain accurate results. There has been no appreciable difference between the sexes in civilian treatment of TBI with HBOT 1.5.

Inclusion Criteria

a. Any 18-65 year-old patient with mild-moderate TBI or PTSD. (If a military injury, subject may be

active duty or a veteran. Subjects with PTSD only will be enrolled because of military medicine's difficulty in distinguishing between these patients. Also, DOD medical or Veteran's Administration disability boards will give a PTSD designation before a TBI designation because the disability rating payment scale is less for PTSD than for TBI.)

b. Have demonstrated a >20% decrement (compared to pre-deployment baseline) in ANAM composite score or specific sub-score with regard to "simple reaction time" and/or "procedural reaction time".
c. Have a diagnosis of TBI, chronic TBI/PCS or TBI/PCS/PTSD or PTSD made by a military (military etiology of blast injury) or civilian neurologist (and neuropsychologist).
d. Negative pregnancy test in females.
e. Less than 90% on the Percent Back to Normal Rating Scale. (If patient is considered 100% normal before TBI, patient should be less than 90% normal for entry into the study).

Exclusion Criteria

a. Pulmonary disease that precludes HBOT (e.g., asthma unresponsive to medication, bullous emphysema).
b. Unstable medical conditions that are contraindicated in HBOT (e.g. severe congestive heart failure or heart failure requiring hospital emergency evaluation or admission in the previous year).
c. Severe confinement anxiety (e.g., patients who require anesthesia conscious sedation for MRI or who cannot go in elevators).
d. Pregnancy.
e. Other pre-TBI neurological diagnoses.(seizure disorders, multiple sclerosis, Parkinson's, Lyme, etc.)
f. Participation in another experimental trial with active intervention.
h. High probability of inability to complete the experimental protocol (e.g. terminal condition).
i. Past or current history of mental retardation unless diagnosed post TBI (baseline IQ ≤ 70).
j. Pre- or post-TBI history of systemic illness with impact on central nervous system. (Principal Investigator in consultation with study sponsor Medical Officer will make the ultimate decision).
k. Any pre-existing chronic infection not related to battlefield injuries or government service.

Vulnerable Subjects

All subjects will be legally capable of consenting. No subjects who need 3rd party consent will be enrolled in the study.

Military - special care and precautions: The subjects will have to voluntarily contact participating sites or respond to a recruitment outreach outside of their command.

Homeless - special care and precautions: All state and local laws will be followed as the team works with federal, state and local homeless programs.

i. Other evaluation(s) as needed:

After a patient inquiry is received the office staff, under the supervision of the PI, will do the initial qualifications assessment and then as appropriate, will schedule the patient for a medical interview and examination. After medical examination and final qualification, they will be scheduled within one week to undergo baseline testing (characterization of initial status) and will begin the therapy within two weeks of formal entry into the study.

The subject's baseline will be ascertained by various means. Some of these characterizations will be specific to those patients with a military etiology. For all subjects with a head injury, the subject will be asked to characterize the nature of the injury (time, date, place, circumstances, loss of consciousness, residual symptoms). For those with a blast injury, we will ascertain, for each exposure, the approximate

time, place, distance from the blast, body orientation with regard to the blast, and frequency of exposure. We will determine if there was any loss of consciousness, medical characterization of same, time course of recovery, and residual symptoms.

In addition to above, for military etiology TBI, the patient's diagnosis according to the military physicians will be ascertained, along with any revision during treatment. Specific forms will be used to characterize the military exposure (see below).

Screening
To determine qualification for the study, patients will be questioned by the site investigator (or staff under direct supervision of the PI) using simple screening questions to determine qualification for the study, regarding hyperbaric oxygen therapy, absolute and relative contraindications, and other inclusion and exclusion criteria. Upon their initial medical evaluation, they will then be consented by the site PI and complete the Rivermead Head Injury Questionnaire, the Michigan Alcohol and Drug Screening Tests (MAST & DAST) to characterize the level of substance abuse, the PTSD checklist to identify and verify the presence or absence of PTSD in TBI subjects, the automated tests ANAM and CNSVS. Depending upon the special assets or capabilities at particular locations, some patients may receive specialized neuropsych testing or imaging at the physician's direction. We will collect as part of the study data from other neuropsych testing or imaging. All patients to receive blood analysis before and after treatment of HBOT.

All subjects will proceed to evaluation with the tests to be described below. Subjects will be urine drug tested prior to enrollment and tested for pregnancy (monthly) then will complete QOL questionnaires that are described below. They will undergo neurological exam and hyperbaric medicine exam by the PI. They will be asked if they have had recent pre-post deployment ANAMs, imaging or full neuropsychiatric testing - if so, these data will be collected.

Disability Rating Scale
The Disability Rating Scale is a well-characterized instrument that reliably reflects general outcome in moderate to severe TBI and has been shown to correlate with electrophysiological measures of brain injury.

Hyperbaric Medical Exam
This exam will be performed by the site PI. It will be another layer of screening of the subject for overall fit to the study as well as assessment of hyperbaric medicine exclusions. Patients will also be instructed in how to clear their ears during chamber pressurization.

Neurological Exam
The neurological exam will be performed by the PI. The patients will be questioned for previous neurological disease. Neurological exam will emphasize balance and gait, two functions that have been found to be abnormal on physical exam in patients with mild or moderate chronic TBI.

Then, subjects will begin to undergo HBOT sessions at 1.5 atmospheres absolute (ATA) for 60 minutes once daily, 5d/week. For persons who have to travel, a modified protocol of twice daily for the first two weeks and once per day thereafter six days per week may be followed to shorten the travel expenses.

Subjects will undergo automated testing (ANAM, and CNSVS) neuropsychiatric testing and complete forms needed for monitoring purposes upon enrollment. Testing will be repeated after 20, 40, 60 and 80 hyperbaric treatments. If necessary, some tests may need to be repeated (i.e., ANAM) to stabilize the results from the learning effect.

At the conclusion of 40 HBOT's the subjects will complete the PBNRS. If the score is ≥ 90% the subjects will have a repeat automated psychometric test battery, QOL questionnaires, urine drug testing, and pregnancy testing.

If the PBNRS is < 90% the subjects will have another 20 HBOT's on a 5-6 HBOT/week schedule and repeat the automated tests.

Six months after final HBOT subjects will be questioned by the PI (or by staff under supervision of PI) preferably in-person, or by phone or internet, regarding return to work or school and PBNRS. They will repeat the automated tests at this point.

Long-term follow up beyond this period will be enabled by phone and online automated testing; the patients will be requested to complete the automated tests for up to 2 years.

Alcohol and Drug Abuse Assessment at Baseline and During Treatment / Michigan Alcohol and Drug Screening Tests
MAST & DAST are standardized measure of lifetime and current substance or alcohol abuse or dependence. Patients with severe scores will NOT be excluded from this study if they have past or current histories of significant substance/alcohol dependence or abuse. Higher severity scores are associated with more severe addictive symptoms on this measure, which could confound evaluation of any HBOT treatment effect. They will be tracked as such.

Psychometric Testing
To facilitate the scale of this study and to allow more frequent evaluation, it is necessary to rely primarily upon automated computerized internet-based neuropsychological tests and questionnaires.

Neuropsychological tests and Quality of Life Questionnaires will be administered to each participant. The screening measures will be used to characterize the patients using diagnostic measures used by both the military and civilian diagnosticians.

The neuropsychological tests in this study are utilized for three purposes: 1) as pre-tests to measure each participant's baseline level of neuropsychological functioning including: intellectual functioning, memory, executive abilities, psychomotor speed and coordination, and psychosocial/adaptive functioning prior to HBOT, 2) as post-tests to measure the effects of HBOT on the neuropsychological measures listed above, and 3) to measure constructs which serve as moderators for the effects of HBOT, including IQ, personality, and adaptive functioning.

Since TBI consists of both focal and diffuse injuries, different patterns of cognitive, neurobehavioral, and adaptive functional impairments are found that contribute to heterogeneous courses and outcomes. In our experience HBOT has differential effects on these impairments that vary individually. To capture the heterogeneity of both the TBI and HBOT response, we will use multiple pre- and post-treatment neuro-behavioral and adaptive functional measures.

Imaging
No imaging is done or required as part of this study. We will be careful not to interfere with the patient's medical care except to provide HBOT and automated neuropsychometric testing as part of this study.

If the patient has imaging (recommended by their physician outside of the study) after enrollment, we will make every effort to have the patient undergo the standard set of automated neuropsychological tests (ANAM and CNSVS) again within one week of any imaging studies.

Characterization of Subject's Military Experience and Etiology of Injury

PTSD Checklist PCL-M
The PCL is a 17-item self-report measure of the 17 DSM-IV symptoms of PTSD. Respondents rate how much they were "bothered by that problem in the past month". Items are rated on a 5-point scale ranging from 1 ("not at all") to 5 ("extremely"). PCL is the PCL-M (military). The PCL-M asks about problems in response to "stressful military experiences."

3Q DVBIC
The purpose of this screen is to identify service members who may need further evaluation for mild traumatic brain injury (MTBI). Screen should be used with service members who were injured during combat operations, training missions or other activities. The 3 Question DVBIC TBI Screening Tool, also called The Brief Traumatic Brain Injury Screen (BTBIS), was validated in a small, initial study conducted with active duty service members who served in Iraq/Afghanistan between January 2004 and January 2005.[1]

Combat Exposure Scale (CES)
The Combat Exposure Scale (CES) is a 7-item self-report measure that assesses wartime stressors experienced by combatants. Items are rated on a 5-point frequency, 5-point duration, 4-point frequency or 4-point degree of loss scale. Respondents are asked to respond based on their exposure to various combat situations, such as firing rounds at the enemy and being on dangerous duty. The total CES score is calculated by using a sum of weighted scores, which can be classified into 1 of 5 categories of combat exposure ranging from "light" to "heavy." The CES was developed for easy administration and scoring; it is useful in both research and clinical settings.[2]

Documentation of TBI Cognitive Deficits

Rivermead Post Concussion Symptoms Questionnaire
The Rivermead Post Concussion Symptoms Questionnaire[23] measures the severity of PCS in TBI. It has been shown to reliably identify those patients with chronic cognitive deficits.

Automated Neuropsychological Testing

ANAM
ANAM is a proven computer-based tool designed to detect speed and accuracy of attention, memory, and thinking ability. It records a Service Member's performance through responses provided on a computer.

***CNS Vital Signs*:**
Verbal Memory (VBM) and Visual Memory (VIM) Tests: Vital Signs includes parallel tests of verbal memory (word list learning) and visual memory (figure learning). The tests are virtually identical, but one uses words as stimuli, the other, geometric shapes.

[1] (Schwab, K. A., Baker, G., Ivins, B., Sluss-Tiller, M., Lux, W., & Warden, D. (2006). The Brief Traumatic Brain Injury Screen (BTBIS): Investigating the validity of a self-report instrument for detecting traumatic brain injury (TBI) in troops returning from deployment in Afghanistan and Iraq. *Neurology, 66*(5)(Supp. 2), A235.
[2] (Keane, T., Fairbank, J., Caddell, J., Zimering, R., Taylor, K., & Mora, C., 1989)

Finger Tapping Test (FTT): The FTT is one of the most commonly used tests in neuropsychology, because of its simplicity and reliability, and because it generates relevant data about fine motor control, which is based on motor speed as well as kinesthetic and visual-motor ability (Mitrushina et al., 1999).

Symbol Digit Coding (SDC): The Symbol Digit Modalities Test (SDMT) (Smith & Jones, 1982) is a variant of the Wechsler DSST, but the position of symbols and digits is reversed.

Neither the SDMT nor the DSST are suitable for repeated administration, because subjects are able to remember the code and thus accelerate their performance (Hindmarch, 1980).

The Stroop Test: The modification adopted for CNS Vital Signs uses only four colors/color words (red, green, yellow, blue), and only one key is in play, the space bar.

The Shifting Attention Test (SAT): The Shifting Attention Test (SAT) measures the subject's ability to shift from one instruction set to another quickly and accurately.

The Continuous Performance Test (CPT): The CPT is a measure of vigilance or sustained attention or attention over time (Rosvold & Delgado, 1956). It has been a popular test because of its robust relationship to psychiatric disorders.

Neurobehavioral & Quality of Life (QOL) Questionnaires

PRIME-MD Patient Health Questionnaire (PHQ)

Citation: The PHQ scales, including GAD-7, are free to use in clinical practice, research and education. The PHQ (and PHQ-9) are adapted from PRIME MD TODAY, developed by Drs. Robert L. Spitzer, Kurt Kroenke, and Janet B.W. Williams. Copyright ©1999 Pfizer Inc.

Purpose: The Patient Health Questionnaire (PHQ) is designed to facilitate the recognition and diagnosis of the most common mental disorders in primary care patients. For patients with a depressive disorder, a PHQ Depression Severity Index score can be calculated and repeated over time to monitor change.

Rivermead Post-Concussion Symptoms Questionnaire (see above)

Modified Perceived Quality of Life Scale

MPQOL is a measure of the degree of personal satisfaction with one's level of functioning across several activities of daily living.

'Percent-Back-to-Normal' rating scale (PBNRS)

PBNRS is a global measure of patient self-reported recovery or the degree to which the patient perceives she or he falls between no post-TBI or PTSD recovery (i.e., 0% = not at all back to normal) and complete post-TBI or PTSD recovery (i.e., 100% = complete recovery or back to normal).

'Return to school or work'

This will be assessed by simple questioning.

Neurological Examination

The neurological exam will be performed by the P.I. The patients will be questioned for previous neurological disease. Neurological exam will emphasize balance and gait, two functions that have been found to be abnormal on physical exam in patients with mild or moderate chronic TBI.

Imaging

Imaging is not required for participation; it is optional and may be obtained anywhere. Imaging data obtained elsewhere will be collected and reviewed upon enrollment. However, if imaging is received from patients, the results will stored in the database for potential future study.

c. A person-centered program:
    i. One can see from the individual testing and screening above this clinical trial is person centric.
    ii. Patient, family, and others as appropriate will be informed of actions, their purpose, and results throughout their trial.
    iii. Every individual participating will be told how they did against the goals established for them.
d. A process for initial and ongoing evaluations:
    i. Standardized measurement—see b. above.
    ii. Criteria for terminating therapy—see inclusion/exclusion criteria above. Patient can terminate at any time but they will be encouraged to continue through complete trail unless they fail due to exclusion criteria.
    iii. Satisfaction—participants will provide feedback and be evaluated as identified above.
e. Access to needed medical services and adjunctive therapy services— All procedures and therapy will be done at a hospital certified by the state of Indiana and any medical or adjunctive therapy services required are available.
f. Adequate space, equipment and facilities. All work done in connection with this clinical trial we are conducted at existing hospital(s) that provide adequate space, equipment and facilities. Thousands of Indiana residents receive hyperbaric oxygen therapy today for FDA approved medical conditions in these facilities.

HYPERBARIC OXYGEN THERAPY (HBOT) PROCESS

Subjects will be treated in various types and sizes of hyperbaric chambers. Patients may undergo treatment in either a multiplace or monoplace chamber. The above description is for the 100% monoplace oxygen chamber which will be the most common chamber used in this study since it is the most common chamber in freestanding and hospital-based centers.

Patients will be instructed before treatment on how to equalize the pressure in their middle ears. Once inside the chamber, just after closure of the chamber door and immediately before pressurization, the subject will be instructed to perform the first Valsalva maneuver to pressurize the middle ear space before the initial 1.5 pounds per square inch (psi) start-up pressurization of the chamber that attains air-tight “seal” of the chamber. This maneuver expands the middle ear space and brings the ear space to neutral volume after the compression effect of the initial 1.5 psi seal pressurization.

Pressurization will proceed with 100% oxygen at 1.0 pounds per square inch (psi) per minute, the lowest pressurization rate, to 1.5 ATA (atmospheres absolute) or 7.35 psi and will take approximately 7 minutes. During the entire pressurization the subject will be continuously instructed to “clear his/her ears” using various pressure equalization techniques that they have learned and practiced before chamber entry. Inability to pressure-equalize the middle ear space will immediately truncate pressurization until the subject can equalize pressure. Pressurization will then resume until the final depth of 1.5 ATA is achieved. The subject will be notified when he/she is at treatment depth. The subject will remain at depth for approximately 45 minutes and the subject will be informed of the onset of depressurization which will occur at the same rate as pressurization. The subject will again be instructed to pressure equalize the middle ear space, however, barotrauma is minimized during

decompression since gas expansion in the middle ear space passively vents through the Eustachian Tube to the pharynx. Total hatch-to-hatch dive time will be 60 minutes. The subject will be queried regarding pain and untoward symptoms after this and all subsequent treatments.

DATA ANALYSIS AND MONITORING

Administrative Coordination of All Sites

We anticipate multiple sites may participate. A main Administrative Project Coordinator (APC) will ensure consistency and accuracy among all sites [each site will have its own study coordinator]:

- Assurances: all sites will obtain a Federal Wide Assurance as well as a Department of Defense Assurance/Addendum (if applicable)
- Training: all investigators and key personnel will complete required human subjects and GCP training (CITI) and appropriate protocol-specific training.
- Oversight and Monitoring: the APC will ensure that all required monitoring of the research is scheduled, completed, and documented at the required time schedules.

Site Monitor

The site monitor will perform site/clinical monitoring to assure high quality trial conduct. As such, they will perform:

- On-site monitoring of individual case histories; assess adherence to the protocol; i.e., ensuring that all subjects have gone through the appropriate consenting process and have signed the most current consent documents.
- Ensure the ongoing implementation of appropriate data entry and quality control procedures;
- Conduct a general assessment of GCPs

Data Collection, Storage & Confidentiality

Data collection and management of the master database will be performed using the CareVector Platform™ (CVP). The CVP is accessible via the Web from a site computer. Research data collected by each site will be stored locally on a site hard drive as primary data. Only persons authorized by the site PI will have access to the data on-site, and each site PI will be fully briefed on the rules of confidentiality. Concurrently, data from all sites will also be stored on the CVP, with all patient names encrypted. The only subject identifiers what will be available on-site will be encrypted file names, and these only for audit and analytical purposes.

The platform also allows for the oversight of the process and sites. It has a built in Auditor role that will support data and safety monitoring functions. Security procedures are a built-in aspect of the CVP, with multi-role and multi-site access-controls. Password protection and access privileges are granted by security administrators, each of whom has Department of Defense security clearances and who have built similar systems for DOD and the commercial sectors.

A CareVector server will house the composite database, with a backup copy stored at a remote location. All data are secured, stored and backed up according to state-of-the-art security protocols at both locations.

The platform with the database ensure that all data entered will be available for daily viewing by the co-PIs for analysis, audits, quality control, and for study throughout the trial. Security is provided via 128-bit SSL encryption across all public channels; database encryption of sensitive items such as patient names and passwords; multiple border and edge firewalls; and F5 load balancing, providing

redundancy and 99.9% uptime guarantee. Training and support for the CVP are provided as a part of the orientation process for the study and are a prerequisite for site participation.

RISK – BENEFIT ASSESSMENT

This is a no significant risk study using an existing FDA-cleared HBOT device.
At a recent DOD-DCOE consensus conference on HBOT in TBI, it was the group's consensus that HBOT at 1.5 ATA 100% O2 was completely safe.[3]

General safety considerations and protection against risks
Significant adverse events will be defined as those requiring emergency department evaluation or hospitalization. Pulmonary barotrauma manifest by pneumothorax or air embolism, inner ear barotraumas with round or oval window rupture, and oxygen toxicity manifest by grand mal seizure would be the most serious adverse events, but are unanticipated. An oxygen toxicity seizure is a rare occurrence at high pressures. The low pressure featured in this study has not been reported to cause seizures and has been used to treat childhood seizures in China and in the United States

The most likely anticipated adverse events would be middle ear and sinus barotraumas. They are most common in the young and elderly, neither of which will be subjects in this study. Transient emotional liability is expected in less than 10% of the study group, but is managed with informed consent and bedside counseling.

Secondary gain for malingering and disability
This may be a problem in mild-moderate TBI research, the degree of malingering is difficult to assess. To prevent elimination of bona fide brain injured patients we will include all patients regardless of level of effort/malingering. Some patients may have already been given disability. It is our objective to only determine whether we can improve patients who have been given military or civilian diagnoses of chronic TBI/PCS and/or TBI/PCS/PTSD and which patients with these diagnoses will be susceptible to possible beneficial effects of HBOT. The inclusion of all can provide valuable information on the effectiveness or ineffectiveness of HBOT and identify/characterize those non-responders.

Concern About post-hoc revision of Military Disability Rating
For those who have already been disability rated by the military the subjects will be informed that their test results are private and cannot be accessed to personally identify them and re-rate their disability.

Training effect may improve performance on automated tests
We will employ measures that minimize learning effect. ANAM and CNSVS are designed to compensate for the learning effect using internal methods, such as the presentation of alternate examples. Further, we will have the subject take the test set twice before starting HBOT treatment.

Excessive amount of testing
The multiple tests are necessary due to the heterogeneity of TBI. Since there is no all-inclusive QOL measure, multiple questionnaires are necessary. To undergo the computerized test batteries the total test time is about two hours. This is substantially less than the amount of time for a full psychometric test battery.

Confinement Anxiety
Severely claustrophobic patients will be screened out by the physician before the Rivermead questionnaire is administered. Some of these patients may do fine with larger chambers as available.

[3] DOD "HBOT for TBI" Consensus Conference White Paper, 28 October 2008.

Xanax, as needed, will help those who still have problems, however, this will be discontinued one week before repeat testing.

Automated Cognitive Testing
Automated cognitive testing has limitations. However, when used to monitor change over time, it is valid.

Lack of sham control group
This is an observational study of an off-label use of an FDA-cleared device. This is acceptable because preliminary pilot data results showing efficacy suggest that a sham treatment arm may be unethical, especially since the data demonstrate that the treatment is extremely safe. And, because the first study by Dr. Harch was a pilot, it will be followed by a second single crossover study that is about to begin in parallel with the present study. Longitudinal measures can be analyzed for comparison to baseline. Also, performance of the subjects in this study can be compared to historical data accumulated by the military on the degree of spontaneous improvement over time in their untreated injured population of servicemen and women.

Alternative Methods & Approaches
While there are other therapies that are attempted for TBI and TBI/PTSD, we know of no safe, effective alternative treatment method for traumatic brain injury.

Alternative outcome measures are numerous and formal comprehensive neuropsychiatric testing may be superior to the automated approaches proposed herein. However, due to logistical, funding, and time constraints it is not possible to obtain the most comprehensive neuropsychological analyses or all possible imaging studies and biomarkers. Rather, we will make every effort to collect information on any testing or imaging ordered by the person's physicians in the routine course of their clinical care.

HBOT 1.5 Safety versus Drugs Prescribed Off-Label for PCS & PTSD
When comparing HBOT to the common drugs being prescribed off-label for PTSD and TBI patients, the difference is remarkable. (Only Zoloft is on-label for PTSD. No drugs are approved for PCS or TBI). Many of the anti-depressants have a warning label from the FDA. The actual FDA warning reads, "Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of (insert name of antidepressant) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24…" The age group described by this warning would seem to include a significant number of our brain-injured veterans. Thus, by getting this study done quickly, the investigators have a good chance of helping reduce the epidemic of suicides in the current population of casualties from the current war.

Potential benefits to the subjects
The subjects will not be given false assurance that they are likely to benefit from the procedure.

Patients will not be compensated and the study will be patient- or site-funded
The subjects will not be compensated for treatment. Actually, until higher levels of funding become available for this study, the subjects and or the site investigators will have to find private funding for their treatment as outlined in the present study.

Alternatives to participation
Congress has funded $1.9 billion in TBI & PTSD research since 2005. Therefore, the patient may choose to continue to participate in any one of the existing programs for patients with TBI and TBI with

PTSD, using drugs and/or complementary therapies. It should be noted that there is no drug or device currently approved by the FDA to treat TBI or TBI with PTSD.

SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT / ASSENT

Method of Identification and Recruitment
Subjects will be recruited through multiple avenues, particularly through military/ veterans service organizations or media reports. It is anticipated that a majority of the subjects will be former military suffering from TBI and PTSD. Our group anticipates media presentations to recruit subjects for this project.

In addition, PI and the participating hospitals have extensive relationships with professional societies which will be conduits to the target population. Print, radio advertisements/ announcements, and website announcements (the International Brain Research Foundation, the International Hyperbaric Medical Association, the American College for the Advancement of Medicine, the American Association of Health Freedom, the American Association of Physicians and Surgeons and others) will also be used to recruit subjects. Additionally, TBI associations and support groups will be targeted for presentations and announcements. Veterans Treatment Courts and law enforcement agencies and organizations will be contacted and encouraged to communicate the opportunity to participate.

Process of consent
Each subject will be provided the consent form and will be provided at least 24 hours to review, consider, ask questions, and sign the consent form. The subject will be provided a copy of any document they sign and two copies will be made for storage on site and at the central office of the sponsor.

Subject capacity
All subjects will have the capacity to consent to treatment. The rare subject will not be able to read due to an eye injury or brain injury. These subjects will have the consent form read to them twice in the presence of a witness and then, the reader and witness will sign the patient's consent form in lieu of the patient.

Subject/representative comprehension
Referring organizations or volunteer veterans' service organizations will receive a briefing on the study, risks, benefits, etc.

Debriefing procedures
All subjects will be briefed by the investigator or designated personnel in accordance with best medical practices for full disclosure of patient outcomes, anticipated future status, and how to return for more treatment, if desired.

Costs to the subject
The subject is responsible for all costs. You will not be paid for your participation or reimbursed for your time and travel.

Multiple efforts are underway to provide funding from outside sources. At this time, the sponsor does not have the funds to pay for the treatment.

The sponsor will pay for all of the automated neuropsychiatric testing, coordination of the study, and collection of data. If the sponsor or funding source does not pay for the treatments and procedures the patient will be responsible for the costs of the study. It is anticipated that the insurance company will

not cover the costs of the treatments in this protocol, because the protocol is considered experimental.

Medicare, in particular, makes it very clear that they do not cover costs that are incurred as part of a research protocol. This protocol is an observational protocol and the use of HBOT therapy for this condition is considered investigational – this is why the present study is being done.

Ancillary diagnostic testing that is NOT required by the study may be recommended by the subject's physician/s. For purposes of planning and estimation, the subject will be informed of the costs of testing that are NOT required in this study are: psychometric screening, evaluation, and quality of life questionnaires ($1000/exam; subjects who undergo testing by a neuropsychologist will have 2 or 3 of these), MRI of the brain with radiologist's reading ($2,000), SPECT brain imaging with radiologist's reading ($1,750 per SPECT; subjects will have 3 or 4 of these), and functional brain MRI (approximately $2,000 per study; there could be 2-3 of these tests).

The principal investigator will arrange for medical care for any emergency medical problem that the subject may experience as a direct result of their participation in this research. This will be provided on a fee-for-service basis. There are no funds available to pay for any disability, study related, or unforeseen complications that result from participation in this study or for damages such as lost wages, etc.

The costs of testing and treatment that are required for this study are outlined in the budget. There are some tests that may be recommended by the patient's physician, however, these are not part of the study unless expressly stated elsewhere in this consent form. Costs of additional testing, such as EEG, angiograms, MRI, CT, or PET imaging, or Doppler studies should be discussed by the patient with the ordering physician. These tests can vary in cost and may or may not be covered by insurance. These tests are not required for the study.

Payment for participation

Other than expense reimbursements from charities or VA travel or Temporary Duty pay that several active duty military have received, the only payback – as opposed to payment -- to the patient is expected to be a significantly improved life from the acute relief of PCS symptoms and restoration of neural function. There has no need to provide incentive payments for participation. These families and individuals, however, are generally financially incapacitated by their disability and therefore third party payment is needed.

CURRICULUM VITAE

Tracey R. Ikerd MD

Address	0610 N. Pennsylvania #A Indianapolis, Indiana 46280
Date of Birth	September 13, 1961
Place of Birth	Princeton, Indiana

Education

Undergraduate
Butler University
Indianapolis, Indiana
Bachelor of Science 1979-1983

Medical School
Indiana University School of Medicine
Bloomington, Indiana
Doctor of Medicine
1983-1987

Residency

St. Vincent Hospital
Indianapolis, Indiana
Internal Medicine
1987-1990

Fellowship

Ohio State University Hospital
Columbus, Ohio
Infectious Disease
1990-1992

Certification

Diplomat in Internal Medicine
American Board of Internal Medicine
September 12, 1990
No. 134254

Licensure

State of Indiana
Medical Licensing Board
March 29, 1990
No. 01038248

Professional Organizations

American College of Physicians (ACP)
Infectious Disease Society of America (IDSA)
Associate Member

Medical Staff Privileges

St. Vincent Hospital
Indianapolis, Indiana

Riverview Hospital
Noblesville, Indiana

Committees

Infectious Control Committee
Riverview Hospital
Noblesville, Indiana

Infectious Control Committee
St. John's Hospital
Anderson. Indiana

P & T Committee
Riverview Hospital
Noblesville, Indiana

Hospital Staff Appointments

Director Infectious Control
Seton Hospital
Carmel, Indiana

Consultant Infectious Control
Riverview Hospital
Noblesville, Indiana

Director Infectious Control
St. John's Hospital
Anderson, Indiana

Publication

Ikerd TR, Koletar SL: An in vitro test of Fluoroquinolones, Macrolides and Menronidq7ole against Giardia lamblia. Journal of Antimicrobial Chemotherapy; 1993; 31:615-617.

CURRICULUM VITAE

JOHN M. PARIS, III, M.D.

DATE AND PLACE OF BIRTH:

January 19, 1950 – New Albany, Indiana

EDUCATION:

Public School, New Albany, IN	1956-1968
(Valedictorian, Class of 1968)	
(National Merit Scholarship Finalist)	
Brown University, Providence, RI – B.A.	1968-1972
Indiana University School of Medicine – M.D.	1972-1976
Indiana University School of Medicine	
General Surgery Intern	1976-1977
Indiana University School of Medicine	
General Surgery Resident	1977-1979
Indiana University School of Medicine	
General Surgery Chief Resident	1979-1980
Indiana University School of Medicine	
Thoracic & Cardiovascular Surgery Resident	1980-1982
Heinz College, Carnegie Mellon University	
Master of Medical Management	2005-2008

PROFESSIONAL HISTORY:

CorVascMDs, PC, Indianapolis, Indiana
July 1982 to July 2008
Cardiothoracic Surgeon

Riverview Surgery Management Association, President
395 Westfield Road
Noblesville, Indiana 46060
May 11, 2004 to December 31, 2012

My responsibilities included managing a for-profit surgery center performing all cases, including major joint replacement and cardiac surgery, except craniotomies. I had five direct reports, and 57 fte's. I reported to an elected board of director, including five physicians and the Hospital CEO, CFO and one Board Director. Our annual net operating revenue was just under two million dollars, and we out-performed budget in each of the years of my leadership. In addition, I changed the culture of the organization. Prior to my tenure, there was no organized quality measuring system. I instituted a performance based metric for the contracted Anesthesia group as well as the employees. As a direct result, our CMS core measure scores exceeded 98%.

Riverview Health, Chief Medical Officer
395 Westfield Road
Noblesville, Indiana 46060
May 11, 2004 to present

The hospital is licensed for 156 beds. My responsibilities include overseeing hospital and physician quality measures, physician performance issues, and participation in an executive steering group, composed of all vice-president level personnel and CEO. Hospital recognitions awarded during my tenure include the 2010 VHA Leadership Award for Clinical Excellence and Clinical Quality and the2012 Health Grades Patient Safety Excellence Award for patient safety in the top 5% of US hospitals. During my tenure, we have consistently raised expectations for performance. Customarily, hospitals reporting CMS core measure dashboards award "green light" status for 90% compliance. In 2005, we raised our standard to 95% compliance. Shortly thereafter, we raised the standard to 97%, and in Q1 2014, we raised the standard to 99% compliance.

Riverview Medical Group
395 Westfield Road
Noblesville, Indiana 46060
October 1, 2010 to Dec 31, 2013

My responsibilities included quality and financial oversight of a network of 52 employed physicians. My task was to transform this confederation of private practices into an integrated health system. The physician network increased from 30 to 50 physicians in my time as administrator. During this time, I added at-risk money to physician contracts based on quality metrics. During my tenure, I also developed meaningful use grids and standards and I was successful in having 100% of eligible providers certified for the adopt, implement and upgrade portion of MU as well as stage 1 of MU. The organization had grown to the degree that the Board of Trustees decided to establish a management team dedicated solely to the employed physician network, and I returned to my impatient responsibilities.

Accountable Care Consortium of Indianapolis
2012-2014

I was a board member and Secretary/Treasurer of the Board of an affiliation of three hospital systems, St. Vincent Ascension, Community Health Partners and Suburban Health Organization. We were developing a network to participate in non-medicare risk-based contracts. This organization dissolved in May of 2014 for a variety of reasons, all of which are lessons I have valued. First, the organization was too big, without a well-defined governance structure. When decisions needed to be made, there was no clear direction. Second, two of the three partners developed their own risk bearing products and lost interest in a common vehicle. Third, the three organizations lacked a common culture. Currently Riverview Health is developing a partnership with another entity, and I will be a physician board member of that nascent organization.

Franciscan-Riverview Health Accountable Care Organization
2015-present

I serve as Chair of Professional Services Committee and Board member of a Shared Savings traditional Medicare ACO model. The Riverview component serves 5400 covered beneficiaries. We will submit data to CMS detailing of first year bench marks in January 2016.

Noblesville Chamber of Commerce
January 2011- December 2016

The Chamber serves a community of approximately 60,000 residents in central Indiana. During my 6 year term on the Board, the city and surrounding county have grown and developed despite trying economic conditions. We have added job-producing industries to our community. The most recent is a radio-pharmaceutical corporation that has a worldwide customer base. I have served as Board chair for 2014 and 2015. During my tenure, I transformed a negative income stream to budget neutral, with a predicted surplus for 2016.

APPOINTMENTS:

Director, Cardiac Surgery Services, Riverview Hospital, Noblesville, Indiana	2001-2008
Director, Cardiac Transplant Program St. Vincent Hospital and Health Services Indianapolis, Indiana	7/1/86 - 2000
Chair, Institutional Review Board St. Vincent Hospital and Health Services Indianapolis, Indiana	1/1/1995-1/1/2005

PROFESSIONAL POSITIONS:

CorVascMDs, PC	1982 – 2008
President, Riverview Surgery Management Association	5/14/01-12/31/13
Chief Medical Officer, Riverview Hospital	May 2004 – present
Administrator, Riverview Medical Group	10/10-12/13

LICENSURE AND CERTIFICATION:

Medical License, State of Indiana, 1976
Federal License Examination, 1976
American Board of Surgery – Diplomate 1981
American Board of Surgery – Recertification 1990
American Board of Thoracic Surgery – Diplomate 1984
American Board of Thoracic Surgery – Recertified 1993, 2002
Fellow, American College of Physician Executives

HONORS AND AWARDS:

Dean's Scholar, Brown University, 1968
Outstanding Senior Student, Department of Surgery, 1976
Seniors Honors Program, Department of Surgery, 1976
Outstanding Essayist, American College of Surgeons,
Indiana Chapter, 1979

PUBLICATIONS AND SCIENTIFIC PRESENTATIONS:

1. Paris JM and Radigan L: Cryopreservation of Canine Small Intestine for Esophageal Substitution. Submitted to Senior Honors Committee, Department of Surgery, April 1976.

2. Grosfeld JL, Ballantine TVN, and Paris JM: Postoperative Intestinal Obstruction in Infants and Children, A Review of 1,306 Laparotomies. Presented to the Indiana Chapter ACS, May 1977.

3. Grosfeld JL and Paris JM: Gastroesophageal Reflux in Infants and Children. Diagnosis and Management. Presented to Indiana Chapter ACS, May 1979.

4. Madura JA and Paris JM: Transduodenal Sphincteroplasty for Biliary Sphincter Dysfunction: A Review of 18 Cases. Presented to Indiana Chapter ACS, May 1979.

5. Glover JL, Paris JM and Vermillion BD: Aneurysmosis: Diffuse Aneurysmal Degeneration of Distal Arterial System. Presented to Indiana Chapter ACS, May 1980.

6. Madura JA, Jesseph JE and Paris JM: The Nardi Test and Biliary Manometry in the Diagnosis of Pancreaticobiliary Sphincter Dysfunction. Presented to the Central Surgical Society, Dearborn, Michigan, March 5, 1981. Published in Surgery, October 1981.

7. Paris JM: Cardiac Transplantation: Are Recipients Happy? Presented at Shumacker Isch “On the Cutting Edge”, Indianapolis, Indiana, March 2, 1990.

8. Paris JM: Cardiac Transplantation: Candidates, Quality of Life. Presented at Shumacker Isch “On the Cutting Edge II”, Indianapolis, Indiana, February 28, 1992.

9. Heimansohn DA, Robison RJ, Paris JM, Matheny RG, Bogdon J, Shaar CJ: Routine Surveillance Endomyocardial Biopsy: Late rejection After Heart Transplantation. Ann Thorac Surg 1997;64:000-00.

5/2006